

AMENDMENTS TO THE CLAIMS

1. **(Original)** A method of modulating a biological response in a cell, the method comprising contacting the cell with at least one agent that modulates the expression or activity of $\text{Err}\alpha$ or Gabb , wherein the biological response is
 - (a) expression of at least one OXPHOS gene;
 - (b) mitochondrial biogenesis;
 - (c) expression of Nuclear Respiratory Factor 1 (NRF-1);
 - (d) β -oxidation of fatty acids;
 - (e) total mitochondrial respiration;
 - (f) uncoupled respiration;
 - (g) mitochondrial DNA replication;
 - (h) expression of mitochondrial enzymes; or
 - (i) skeletal muscle fiber-type switching.
- 2-16. **(Canceled)**
17. **(Withdrawn - Currently Amended)** A method of determining whether if an agent is a potential agent for the treatment of a disorder that is characterized by glucose intolerance, insulin resistance or reduced mitochondrial function, the method comprising determining whether if the agent increases:
 - (i) the expression or activity of $\text{Err}\alpha$ or Gabb in a cell; or
 - (ii) the formation of a complex between a PGC-1 polypeptide and (i) an $\text{Err}\alpha$ polypeptide; or (ii) a Gabb polypeptide;wherein an agent that increases (i) or (ii) is a potential target for the treatment of the disorder.
18. **(Canceled)**

19. **(Withdrawn)** The method of claim 17, wherein the agent increases the formation of the complex, and wherein the agent increases the biological response.
20. **(Withdrawn)** The method of claim 19, wherein the agent decreases the formation of the complex, and wherein the agent decreases the biological response.
- 21-34. **(Canceled)**
35. **(Original)** A method of reducing the metabolic rate of a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of an agent which decreases the expression or activity of at least one of the following:
- (i) $Err\alpha$;
 - (ii) $Gabpa$;
 - (iii) a gene having an $Err\alpha$ binding site, a $Gabpa$ binding site, or both; or
 - (iv) a transcriptional activator which binds to an $Err\alpha$ binding site or to a $Gabpa$ binding site;
- thereby reducing the metabolic rate of the patient.
- 36-41. **(Canceled)**
42. **(Withdrawn - Currently Amended)** A method of identifying a susceptibility locus for a disorder that is characterized by reduced mitochondrial function, glucose intolerance, or insulin intolerance in a subject, the method comprising
- (i) identifying at least one polymorphism ~~polymorphisms~~ in a gene, or linked to a gene, wherein the gene (a) has an $Err\alpha$ binding site, a $Gabpa$ binding site, or both; or (b) is $Err\alpha$, $Gabpa$, or $Gabpb$;
 - (ii) determining whether if at least one polymorphism is associated with the incidence of the disorder,
- wherein if a polymorphism is associated with the incidence of the disorder then the gene having the polymorphism, or the gene to which the polymorphism is linked, is a susceptibility locus.

43-46. (Canceled)

47. **(Withdrawn -Currently Amended)** A method of determining whether if a subject is at risk of developing a disorder which is characterized by reduced mitochondrial function, the method comprising determining whether if a gene from the subject contains a mutation which reduces the function of the gene, wherein the gene has an $\text{Err}\alpha$ binding site, a Gapba binding site, or both, wherein if a gene from the subject contains the mutation then the subject is at risk of developing the disorder.

48-77. (Canceled)

78. **(Withdrawn -Currently Amended)** A method of detecting statistically-significant differences in the expression level of at least one biomarker belonging to a biomarker set, between the members of a first and of a second experimental group, comprising:

- (a) obtaining a biomarker sample from members of the first and the second experimental groups;
- (b) determining, for each biomarker sample, the expression levels of at least one biomarker belonging to the biomarker set and of at least one biomarker not belonging to the set;
- (c) generating a rank order of each biomarker according to a difference metric of its expression level in the first experimental group compared to the second experimental group;
- (d) calculating an experimental enrichment score for the biomarker set by applying a non-parametric ~~non-parametric~~ statistic; and
- (e) comparing the experimental enrichment score with a distribution of randomized enrichment scores to calculate the fraction of randomized enrichment scores greater than the experimental enrichment score, wherein a low fraction indicates a statistically-significant difference in the expression level of the biomarker set between the members of the first and of the second experimental group.

79-92. (Canceled)

93. **(Currently Amended)** A method of identifying an agent that regulates expression of OXPHOS-CR genes, the method comprising
- (a) contacting (i) an agent to be assessed for its ability to regulate expression of OXPHOS-CR genes with (ii) a test cell; and
 - (b) determining whether the expression of at least two OXPHOS-CR gene products show a coordinate increase~~change~~ in the test cell compared to an appropriate control, wherein a coordinate increase~~change~~ in the expression of the OXPHOS-CR gene products indicates that the agent regulates the expression of OXPHOS-CR genes.

94-105. (Canceled)

106. **(Currently Amended)** The method of claim 93, wherein a coordinate increase~~change~~ in the expression of the OXPHOS-CR gene products further indicates that the agent is a potential enhancer~~modulator~~ of the expression or activity of $\text{Err}\alpha$ or $\text{G}\alpha\text{bp}$.
107. **(Currently Amended)** The method of claim 106, wherein a coordinate increase~~change~~ in the expression of the OXPHOS-CR gene products further indicates that the agent is a potential agent for enhancing ~~modulating~~ mitochondrial biogenesis, expression of Nuclear Respiratory Factor 1 (NRF-1), β -oxidation of fatty acids, total mitochondrial respiration, uncoupled respiration, mitochondrial DNA replication, expression of mitochondrial enzymes, or skeletal muscle fiber-type switching.
108. **(Currently Amended)** The method of claim 93, wherein the agent to be assessed is a small molecule~~method comprises determining whether the expression of at least two OXPHOS-CR gene products show a coordinate increase in the test cell as compared to an appropriate control~~.

109. **(Currently Amended)** The method of claim 93 ~~108~~, wherein a coordinate increase in the expression of the OXPHOS-CR gene products indicates that the agent is a potential agent for the treatment of a disorder that is characterized by glucose intolerance, insulin resistance or reduced mitochondrial function.
110. **(Currently Amended)** The method of claim 93 ~~108~~, wherein a coordinate increase in the expression of the OXPHOS-CR gene products further indicates that the agent is a potential agent for increasing expression or activity of $\text{Err}\alpha$ or Gapb .
111. **(Previously Presented)** The method of claim 110, wherein an agent that increases expression or activity of $\text{Err}\alpha$ or Gapb is a potential agent for the treatment of a disorder that is characterized by glucose intolerance, insulin resistance or reduced mitochondrial function.
112. **(Currently Amended)** The method of claim 110, wherein the test cell is a mammalian cell ~~a coordinate increase in the expression of the OXPHOS-CR gene products indicates that the agent is a potential agent for increasing mitochondrial biogenesis, expression of Nuclear Respiratory Factor-1 (NRF-1), β -oxidation of fatty acids, total mitochondrial respiration, uncoupled respiration, mitochondrial DNA replication, expression of mitochondrial enzymes, or skeletal muscle fiber type switching.~~
113. **(Withdrawn)** The method of claim 93, further comprising assessing the effect of the agent on mitochondrial number or on a mitochondrial function.
114. **(Withdrawn)** The method of claim 93, further comprising assessing whether the agent increases a desired biological response that is impaired in subjects having a disorder that is characterized by glucose intolerance, insulin resistance, or decreased mitochondrial function.
115. **(Withdrawn - Currently Amended)** The method of claim 93, wherein step (a) is performed in vitro, and the method further comprises ~~comprising~~ administering the agent to a mammalian organism.

- 116. **(Withdrawn)** The method of claim 115, wherein the mammalian organism is human.
- 117. **(Withdrawn)** The method of claim 115, wherein the mammalian organism is a test animal that serves as a model for a disorder characterized by glucose intolerance, insulin resistance, or decreased mitochondrial function.
- 118. **(New)** The method of claim 93, wherein the test cell is a mammalian cell.
- 119. **(New)** The method of claim 118, wherein the test cell is a skeletal muscle cell.
- 120. **(New)** The method of claim 118, wherein the test cell is in an organism.
- 121. **(New)** The method of claim 118, wherein the agent to be assessed is a small molecule.
- 122. **(New)** The method of claim 93, wherein the method is performed in parallel on multiple populations of cells and each population is contacted with a different agent to be assessed.
- 123. **(New)** The method of claim 122, wherein the agents are members of a compound library.
- 124. **(New)** The method of claim 109, wherein the agent is useful for treating a human suffering from a disorder that is characterized by glucose intolerance, insulin resistance or reduced mitochondrial function.
- 125. **(New)** The method of claim 111, wherein the agent is useful for treating a human suffering from a disorder that is characterized by glucose intolerance, insulin resistance or reduced mitochondrial function.
- 126. **(New)** The method of claim 93, further comprising determining whether the agent also regulates expression of genes that are not OXPHOS-CR genes.